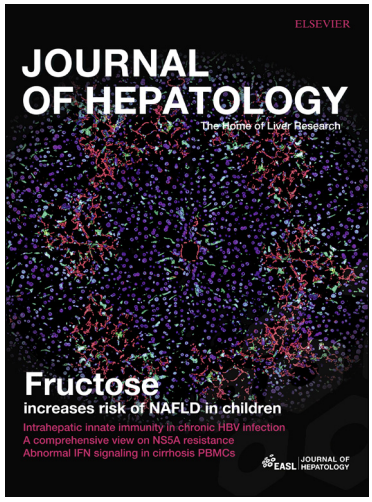

"DCD consensus and futility in Liver Transplantation"

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Title Page:

Title: **"DCD consensus and futility in Liver Transplantation"**

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Schlegel A et al. describe a newly formulated donation after cardiac death (DCD) liver transplantation predictive index, which may redefine futility in DCD liver transplantation[1]. Death on the waiting list and organ scarcity have encouraged the use of "marginal" grafts, a term that encompasses the DCD liver[1]. Contrary to the initial reports, mounting experience from centers with high volume DCD programs demonstrate that DCD vs. donation after brain death (DBD) graft survival equivalence can be attained[2-4]. Understanding how this is achieved is fundamental to standardizing the risk of DCD liver transplantation. The authors are to be congratulated on their DCD predictive model and the utilization of large datasets from National Health Service Blood and Transplant (NHSBT) and United Network for Organ Sharing (UNOS) for validation. They demonstrate seven parameters (donor age, donor BMI, functional warm ischemic time, cold ischemic time, laboratory MELD, recipient age and retransplantation status), which can be objectively determined prior to implantation to be associated with DCD futility. Many of these factors are acknowledged variables for graft survival and are already used by the clinician when judging graft suitability for a given recipient.

It is interesting that this DCD Risk Score model has been validated on the UNOS database, considering the significant variability in organ procurement techniques across USA transplant programs, lack of consensus on donor fWIT and varying DCD withdrawal protocols. For example, in the USA, withdrawal of life support commonly occurs in the operating room and heparin is routinely given prior to

withdrawal. This is in contrast to UK practice where withdrawal occurs in the anaesthetic room or at the intensive care unit and heparin is only given after death in organ preservation fluid. Additional organ procurement events with potentially significant impact on graft outcome, such as endobiliary flush for cholangiopathy minimization and short donor hepatectomy times, are typically unaccounted for variables when comparing International DCD datasets.

Another aspect that adds to the complexity in developing a globally applicable DCD predictive model is that definitions of time intervals that are potentially critical to the outcome, such as the donor functional warm ischemic time (fWIT), vary widely. The inconsistency in definitions and terminology in DCD donation had already been identified and had resulted in the establishment of the European Working Group in 2012 including experts from the UK, Spain, France and Eurotransplant, supported by the European Commission. Aim of the Working Group was to conclude to a consensus agreement on the definitions and terminology regarding DCD organ donation. Their work was presented at the 6th International Conference on Organ Donation after Circulatory Death held in Paris in 2013[5]. This has certainly facilitated more consistent usage of terms in DCD donation. Nevertheless, fWIT recording, definition and acceptable range remain variable and dependent upon the organ procurement teams. For example, King's fWIT definition is from oxygen saturation of 70% and/or systolic of 50mmHg or less to aortic cannulation. Many others will base start of donor fWIT on systolic pressure alone or from time of withdrawal to aortic cannulation. Stringency on

donor fWIT appears to be an important element of cholangiopathy minimization[6,7].

In all three DCD predictive models described (UCLA, Kings, Birmingham), four variables are shared: fWIT, cold ischemic time (CIT), recipient laboratory MELD, and re-transplantation[1, 7, 8]. Both UCLA and Kings included HCV status, but this parameter is already becoming obsolete in the era of direct acting antivirals. Normothermic machine perfusion might further mitigate the insult of prolonged fWIT and CIT to the DCD graft outcome, but this is yet to be elucidated. King's DCD model further stratified risk according to underlying liver failure etiology, which might purely reflect primary liver disease recurrence risk, but may also represent the influence of recipient milieu/disease status on regenerative/recovery capacity of the DCD liver. Similarly, the use of laboratory MELD in all of these DCD models maybe regarded as a surrogate marker for a favorable recipient environment for liver recovery. Highlighting that the cellular basis of liver recovery/regeneration in transplant still remains ill understood, as no additional objective measure of this aspect has yet to be introduced into clinical practice.

The wording of futility has to be used in carefully in liver transplantation, for most it means less than 50% survival at 5 years. All authors agree that retransplantation increases graft loss risk after DCD transplant. But inferior survival in liver retransplantation is well established[9, 10]. It may be worthwhile to

confirm if retransplantation survival is inferior after DCD as opposed to DBD liver transplantation, independently of CIT. In some recipients awaiting retransplantation, the window of opportunity is small and then the only chance of survival remains with a DCD liver. Another inherent limitation in all the developed DCD predictive models is that they are founded on skewed datasets as clinicians already balance the donor recipient risk. Additionally, steatosis has not been included in any of the models and in routine practice liver steatosis is a common reason for DCD liver decline; the assessment of which remains highly subjective and not related to the functional capacity of the liver.

To move DCD liver transplantation forward there needs to be a standardization of practice, nomenclature and data collection. However, all of the DCD predictive models developed to date do confirm that the fundamental principles of good outcome after DCD liver transplantation are based on fastidious donor procurement, attention to ischemic times (warm/cold) and recipient selection. Ultimately, the addition of objective tests that define the functional/recovery capacity of the DCD liver will give foundation to donor recipient algorithms of the future.

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